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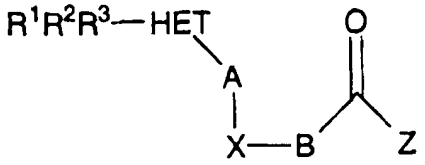

(I)

(57) Abstract

Compounds of formula (I), as well as pharmaceutically acceptable salts, hydrates and esters thereof, are disclosed. The compounds are useful for treating or preventing prostaglandin mediated diseases. Pharmaceutical compositions containing such compounds and methods of treatment are also included.

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CARBOXYLIC ACIDS AND ACYLSULFONAMIDES, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF TREATMENT

BACKGROUND OF THE INVENTION

The present invention relates to compounds which are useful for treating or preventing prostaglandin mediated diseases, methods of treatment and pharmaceutical compositions containing such compounds. The compounds are structurally different from conventional NSAIDs and opiates, and are antagonists of the pain and inflammatory effects of E-type prostaglandins.

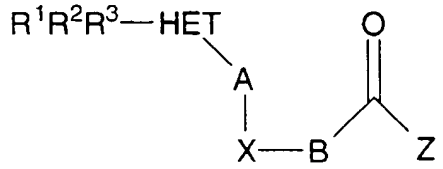
Two review articles describe the characterization and therapeutic relevance of the prostanoid receptors as well as the most commonly used selective agonists and antagonists: *Eicosanoids: From Biotechnology to Therapeutic Applications*, Folco, Samuelsson, Maclouf, and Velo eds, Plenum Press, New York, 1996, chap. 14, 137-154 and Journal of Lipid Mediators and Cell Signalling, 1996, 14, 83-87. An article from *The British Journal of Pharmacology* (1994, 112, 735-740) suggests that Prostaglandin E_2 (PGE_2) exerts allodynia through the EP_1 receptor subtype and hyperalgesia through EP_2 and EP_3 receptors in the mouse spinal cord.

Thus, selective prostaglandin ligands, agonists or antagonists, depending on which prostaglandin E receptor subtype is being considered, have anti-inflammatory, antipyretic and analgesic properties, and in addition inhibit hormone-induced uterine contractions. Moreover, the compounds have anti-cancer effects.

The compounds have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

SUMMARY OF THE INVENTION

The present invention relates to compounds represented by formula I:



I

as well as pharmaceutically acceptable salts, hydrates and esters thereof, wherein:

HET represents a 5-12 membered monocyclic or bicyclic aromatic ring system containing 0-3 heteroatoms selected from O, $S(O)_n$ and $N(O)_m$ wherein m is 0 or 1 and n is 0, 1 or 2;

A is a one or two atom moiety and is selected from the group consisting of: -W-, -C(O)- , $-C(R^7)_2$-W- , -W-$C(R^7)_2$ - , $-CR^7(OR^{20})$- , $-C(R^7)_2$ - , $-C(R^7)_2$-$C(OR^{20})R^7$ - , $-C(R^7)_2$- $C(R^7)_2$- or $-CR^7=CR^7$- , wherein W represents O, $S(O)_n$ or NR^{17}, with n as previously defined and R^{17} as defined below;

X represents a 5-10 membered monocyclic or bicyclic aryl or heteroaryl group having 1-3 heteroatoms selected from O, $S(O)_n$ and $N(O)_m$, and optionally substituted with R^{14} and R^{15}, and A and B are attached to the aryl or heteroaryl group ortho relative to each other;

Y represents O, $S(O)_n$, NR^{17}, a bond or $-CR^{18} = CR^{18}$- ;

B represents - $(C(R^{18})2)_p$-Y- $(C(R^{18})2)_q$ -

wherein p and q are independently 0-3, such that when Y represents O, $S(O)_n$, NR^{17} or $-CR^{18} = CR^{18}$- , p + q = 0-6, and when Y represents a bond, p + q is 1-6;

Z is OH or $NHSO_2R^{19}$;

R^1 R^2 and R^3 independently represent H, halogen, lower alkyl, lower alkenyl, lower alkynyl, lower alkenyl-$HET(R^a)_{4-9}$, - $(C(R^4)2)_pSR^5$, $-(C(R^4)_2)_pOR^8$, $-(C(R^4)_2)_pN(R^6)_2$, CN, NO_2, $-(C(R^4)_2)_pC(R^7)_3$, - CO_2R^9, $-CON(R^6)_2$ or $-(C(R^4)_2)_pS(O)_nR^{10}$, wherein n and p are as previously defined;

each R^4 is independently H, F, CF_3 or lower alkyl,

or two R^4 groups are taken in conjunction and represent a ring of up to six atoms, optionally containing one heteroatom selected from O, $S(O)_n$ or $N(O)_m$;

each R^5 is independently lower alkyl, lower alkenyl, lower alkynyl, CF_3, lower alkyl-HET, lower alkenyl-HET or $-(C(R^{16})_2)_pPh(R^{11})_{0-2}$;

each R^6 is independently H, lower alkyl, lower alkenyl, lower alkynyl, CF_3, Ph, Bn and when two R^6 groups are attached to N they may be taken in conjunction and represents a ring of up to 6 atoms, optionally containing an additional heteroatom selected from O, $S(O)_n$ or $N(O)_m$;

each R^7 is independently H, F, CF_3 or lower alkyl, and when two R^7 groups are presents, they may be taken in conjunction and represent an aromatic or aliphatic ring of 3 to 6 members containing from 0-2 heteroatoms selected from O, $S(O)_n$ and $N(O)_m$;

each R^8 represents H or R^5;

each R^9 is independently H, lower alkyl, lower alkenyl, lower alkynyl, Ph or Bn;

each R^{10} is independently lower alkyl, lower alkenyl, lower alkynyl, CF_3, $Ph(R^{11})_{0-3}$, $CH_2Ph(R^{11})_{0-3}$ or $N(R^6)_2$;

each R^{11} is independently lower alkyl, SR^{20}, OR^{20}, $N(R^6)_2$, $-CO_2R^{12}$, $-CON(R^6)_2$, $-C(O)R^{12}$, CN, CF_3, NO_2 or halogen;

each R^{12} is independently H, lower alkyl or benzyl;

each R^{13} is independently H, halo, lower alkyl, O-lower alkenyl, S-lower alkyl, $N(R^6)_2$, CO_2R^{12}, CN, CF_3 or NO_2 ;

R^{14} and R^{15} are independently lower alkyl, halogen, CF_3, OR^{15}, $S(O)_nR^{16}$ or $C(R^{16})_2OR^{17}$;

each R^{16} is independently H, lower alkyl, lower alkenyl, Ph, Bn or CF_3;

each R^{17} is independently H, lower alkyl or Bn;

each R^{18} is independently H, F or lower alkyl, and when two R^{18} groups are present, they may be taken in conjunction and represent a ring of 3 to 6 members comprising carbon atoms and optionally one heteroatom chosen from O, $S(O)_n$ or N;

each R^{19} is lower alkyl, lower alkenyl, lower alkynyl, CF_3, $HET(R^a)_{4-9}$, lower alkyl-$HET(R^a)_{4-9}$ or lower alkenyl-$HET(R^a)_{4-9}$;

each R^{20} is independently H, lower alkyl, lower alkenyl, lower alkynyl, CF_3 or $Ph(R^{13})_2$

and

each R^a is independently selected from the group consisting of:

H, OH, halo, CN, NO_2, amino, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6} alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkylamino, di-C_{1-6}alkylamino, CF_3, $C(O)C_{1-6}$alkyl, $C(O)C_{2-6}$alkenyl, $C(O)C_{2-6}$alkynyl, CO_2H, CO_2C_{1-6}alkyl, CO_2C_{2-6}alkenyl, CO_2C_{2-6}alkynyl, and CO_2C_{2-6}alkynyl,

said alkyl, alkenyl, alkynyl and the alkyl portions of alkylamino and dialkylamino being optionally substituted with 1-3 of: hydroxy, halo, aryl, C_{1-6} alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, CF_3, $C(O)C_{1-6}$alkyl, $C(O)C_{2-6}$alkenyl, $C(O)C_{2-6}$alkynyl, CO_2H, CO_2C_{1-6}alkyl, CO_2C_{2-6}alkenyl, CO_2C_{2-6}alkynyl, NH_2, NHC_{1-6}alkyl and $N(C_{1-6}$alkyl$)_2$.

Pharmaceutical compositions are also included which are comprised of a compound of formula I in combination with a pharmaceutically acceptable carrier.

A method of treating or preventing a prostaglandin mediated disease is also included which is comprised of administering to a mammalian patient in need thereof, a compound of formula I in an amount which is effective for treating or preventing a prostaglandin mediated disease.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to carboxylic acids and acylsulfonamides, which are ligands at prostaglandin receptors, as well as a method for treating or preventing a prostaglandin mediated disease comprising administering to a patient in need of such a treatment of an amount of compound of Formula I which is effective for treating or preventing a prostaglandin mediated disease.

The invention described in this patent application is described using the following definitions unless otherwise indicated.

HET represents a 5-12 membered aromatic ring system containing 0-3 heteroatoms selected from O, $S(O)_n$ and N wherein n is 0, 1 or 2. HET may be substituted with up to three substituents on the aromatic ring system, R^1, R^2 and R^3. "Aromatic ring systems" as used herein includes aryl and heteroaryl groups such as benzene, naphthalene, biphenyl, pyridine, quinoline, isoquinoline, furan, benzofuran, thiophene, benzothiophene, oxazole, thiazole, imidazole, benzothiazole, triazole, 1,2,5-thiadiazole, thienopyridine, indole, tetrazole, imidazole, benzoxazole, 1,2-methylenedioxybenzene and pyrrole.

HET^2 is a subset of HET and represents a member selected from the group consisting of: phenyl, thienyl, naphthyl, furanyl, thiazolyl, imidazolyl and indolyl.

Aryl refers to aromatic 6-10 membered groups having 1-2 rings and alternating (resonating) double bonds. Examples include phenyl, biphenyl and naphthyl.

Heteroaryl refers to aromatic 5-12 membered groups having alternating (resonating) double bonds and containing from 1-4 heteroatoms selected from O, $S(O)_n$ and N. Examples include the following: : quinoline, furan, benzofuran, thiophene, benzothiophene, thiazole, benzothiazole, 1,2,5-thiadiazole, thienopyridine, oxazole, indole, isoindole, pyridine, isoquinoline, imidazole, thiazole, triazole, 1,3-methylene dioxobenzene, pyrrole and naphthyridine,

Heterocyclyl refers to non-aromatic 5-12 membered cyclic groups having 1-4 heteroatoms selected from O, $S(O)_n$ and N. Examples of heterocyclic groups are piperidine, piperazine, pyrrolidine, tetrahydrofuran, tetrahydropyran and morpholine.

X represents a 5-10 membered monocyclic or bicyclic aryl or heteroaryl group having 1-3 heteroatoms selected from O, $S(O)_n$ and $N(O)_m$, and optionally substituted with R^{14} and R^{15}, and A and B are attached to the aryl or heteroaryl group X in positions which are ortho relative to each other. Examples are selected from the group consisting of: phenyl, naphthyl, biphenyl, quinoline, furan, benzofuran, pyridyl, pyrrole, thiophene, benzothiophene, thiazole, benzothiazole, 1,2,5-

thiadiazole, triazole, 1,2-methylenedioxybenzene, thienopyridine, oxazole and indole.

The terms alkyl, alkenyl, and alkynyl mean linear, branched, and cyclic structures and combinations thereof.

"Lower alkyl" means alkyl groups of from 1 to 7 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, cyclopropyl, isopropyl, butyl, s- and t-butyl, pentyl, cyclopentyl, hexyl, cyclohexyl, heptyl, and the like. When propyl and butyl are recited without the isomeric form being specified, these include all isomers thereof.

"Lower alkenyl" means alkenyl groups of 2 to 7 carbon atoms. Examples of lower alkenyl groups include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, cyclopropen-1-yl, cyclohexen-3-yl and the like. When cis or trans is not specified, both are intended in pure form as well as in the form of a mixture of isomers.

"Lower alkynyl" means alkynyl groups of 2 to 7 carbon atoms. Examples of lower alkynyl groups include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl, 2-(cyclopropyl)ethenyl, 3-(cyclobutyl)-1-propynyl and the like.

Halogen (halo) includes F, Cl, Br and I.

The following abbreviations have the indicated meanings:

AIBN	=	2.2'-azobisisobutyronitrile
B.P.	=	benzoyl peroxide
Bn	=	benzyl
CCl_4	=	carbon tetrachloride
D	=	$-O(CH_2)_3O-$
DAST	=	diethylamine sulfur trifluoride
DCC	=	dicyclohexyl carbodiimide
DCI	=	1-(3-dimethylaminopropyl)-3-ethyl carbodiimide
DEAD	=	diethyl azodicarboxylate
DIBAL	=	diisobutyl aluminum hydride
DME	=	ethylene glycol dimethylether
DMAP	=	4-(dimethylamino)pyridine
DMF	=	N,N-dimethylformamide
DMSO	=	dimethyl sulfoxide
Et_3N	=	triethylamine
LDA	=	lithium diisopropylamide

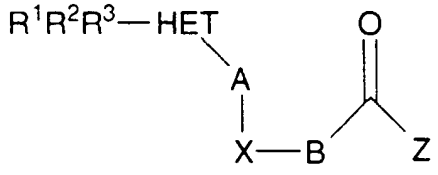
	m-CPBA	=	metachloroperbenzoic acid
	NBS	=	N-bromosuccinimide
	NSAID	=	non-steroidal anti-inflammatory drug
	PCC	=	pyridinium chlorochromate
	PDC	=	pyridinium dichromate
	Ph	=	phenyl
	1,2-Ph	=	1,2-benzenediyl
	Pyr	=	pyridinediyl
	Qn	=	7-chloroquinolin-2-yl
	Rs	=	$-CH_2SCH_2CH_2Ph$
	r.t.	=	room temperature
	rac.	=	racemic
	THF	=	tetrahydrofuran
	THP	=	tetrahydropyran-2-yl

Alkyl group abbreviations

Me	=	methyl
Et	=	ethyl
n-Pr	=	normal propyl
i-Pr	=	isopropyl
n-Bu	=	normal butyl
i-Bu	=	isobutyl
s-Bu	=	secondary butyl
t-Bu	=	tertiary butyl
c-Pr	=	cyclopropyl
c-Bu	=	cyclobutyl
c-Pen	=	cyclopentyl
c-Hex	=	cyclohexyl

It is intended that the definition of any substituent (e.g., R^5, R^6, etc.) in a particular molecule be independent of its definition elsewhere in the molecule. Thus, $-N(R^6)_2$ represents -NHH, $-NHCH_3$, $-NHC_6H_5$, and the like.

In one aspect of the invention, the invention relates to a compound represented by formula I:



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as well as pharmaceutically acceptable salts, hydrates and esters thereof, wherein:

HET represents a 5-12 membered monocyclic or bicyclic aromatic ring system containing 0-3 heteroatoms selected from O, $S(O)_n$ and $N(O)_m$ wherein m is 0 or 1 and n is 0, 1 or 2;

A is a one or two atom moiety and is selected from the group consisting of: -W-, -C(O)- , $-C(R^7)_2$-W- , -W-$C(R^7)_2$ - , $-CR^7(OR^{20})$- , $-C(R^7)_2$ - , $-C(R^7)_2$-$C(OR^{20})R^7$ - , $-C(R^7)_2$- $C(R^7)_2$ or CR^7=CR^7, wherein W represents O, $S(O)_n$ or NR^{17}, with n as previously defined and R^{17} as defined below;

X represents a 5-10 membered monocyclic or bicyclic aryl or heteroaryl group having 1-3 heteroatoms selected from O, $S(O)_n$ and $N(O)_m$, and optionally substituted with R^{14} and R^{15}, and A and B are attached to the aryl or heteroaryl group ortho relative to each other;

Y represents O, $S(O)_n$, NR^{17}, a bond or $-CR^{18} = CR^{18}-$;

B represents $-(C(R^{18})_2)_p$-Y-$(C(R^{18})_2)_q$ -

wherein p and q are independently 0-3, such that when Y represents O, $S(O)_n$, NR^{17} or $-CR^{18} = CR^{18}-$, p + q = 0-6, and when Y represents a bond, p + q is 1-6;

Z is OH or $NHSO_2R^{19}$;

R^1 R^2 and R^3 independently represent H, halogen, lower alkyl, lower alkenyl, lower alkynyl, lower alkenyl-$HET(R^a)_{4-9}$, $-(C(R^4)_2)_pSR^5$, $-(C(R^4)_2)_pOR^3$, $-(C(R^4)_2)_pN(R^6)_2$, CN, NO_2, $-(C(R^4)_2)_pC(R^7)_3$, $-CO_2R^9$, $-CON(R^6)_2$ or $-(C(R^4)_2)_pS(O)_nR^{10}$, wherein n and p are as previously defined;

each R^4 is independently H, F, CF_3 or lower alkyl, or two R^4 groups are taken in conjunction and represent a ring of up to six atoms, optionally containing one heteroatom selected from O, $S(O)_n$ or $N(O)_m$;

each R^5 is independently lower alkyl, lower alkenyl, lower alkynyl, CF_3, lower alkyl-HET, lower alkenyl-HET or $-(C(R^{18})_2)_pPh(R^{11})_{0-2}$.

each R^6 is independently H, lower alkyl, lower alkenyl, lower alkynyl, CF_3, Ph, Bn and when two R^6 groups are attached to N they may be taken in conjunction and represents a ring of up to 6 atoms,

$R^1R^2R^3$-Het	A	X	B	Cpd
2-(benzo[b]thiophenyl)	CH_2	4-F-1,2-Ph	CH=CH	539
5-(1-benzyl)indolyl	CH_2	4-F-1,2-Ph	CH=CH	540
1-(6-(4-chloro)phenyl) indolyl	CH_2	4-F-1,2-Ph	CH=CH	541
1-(5-chloro)indolyl	CH_2	3,2-Pyr	CH=CH	542

wherein D= $-O(CH_2)_3-O$, Qn= 7-chloroquinolin-2-yl, 1,2-Ph = 1,2-benzenediyl, Rs = $-CH_2SCH_2CH_2Ph$, Pyr = pyridinediyl, c-pr = cyclopropyl and Bn = benzyl.

19. A pharmaceutical composition which is comprised of a compound in accordance with any one of claims 1 to 18 in combination with a pharmaceutically acceptable carrier.

20. A method of treating or preventing a prostaglandin mediated disease which is comprised of administering to a mammalian patient in need of such treatment a compound in accordance with claim 1 in an amount which is effective for treating or preventing a prostaglandin mediated disease.

21. A method in accordance with claim 19 wherein the prostaglandin mediated disease is selected from the group consisting of:

pain, fever or inflammation associated with rheumatic fever, influenza or other viral infections, common cold, low back and neck pain, skeletal pain, post-partum pain, dysmenorrhea, headache, migraine, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns including radiation and corrosive chemical injuries, sunburns, pain following surgical and dental procedures, immune and autoimmune diseases;

cellular neoplastic transformations or metastic tumor growth;

diabetic retinopathy, tumor angiogenesis;

prostanoid-induced smooth muscle contraction associated with dysmenorrhea, premature labor, asthma or eosinophil related disorders;

Alzheimer's disease;

glaucoma;

bone loss;

osteoporosis;

promotion of bone formation;

Paget's disease;

cytoprotection in peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or other gastrointestinal lesions; GI bleeding and patients undergoing chemotherapy;

coagulation disorders selected from hypoprothrombinemia, haemophilia and other bleeding problems;

kidney disease;

thrombosis;

occlusive vascular disease;

presurgery;

and anti-coagulation.

22. A method in accordance with claim 20 wherein the prostaglandin mediated disease is selected from the group consisting of: pain, fever or inflammation.

23. A method in accordance with claim 20 wherein the prostaglandin mediated disease is dysmenorrhea.

24. A method in accordance with claim 20, wherein the compound is co-administered with other agents or ingredients.

25. A method in accordance with claim 24 wherein the compound I is co-administered with another agent or ingredient selected from the group consisting of: an analgesic selected from acetaminophen, phenacetin, aspirin, a narcotic;

a COX-2 selective NSAID and a conventional NSAID;

caffeine;

an H_2-antagonist;

aluminum or magnesium hydroxide;

simethicone;

a decongestant selected from phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine;

an antiitussive selected from codeine, hydrocodone, caramiphen, carbetapentane and dextramethorphan;

another prostaglandin ligand selected from misoprostol, enprostil, rioprostil, ornoprostol and rosaprostol; a diuretic; and

a sedating or non-sedating antihistamine.

26. Use of a compound, salt, hydrate or ester as defined in any one of claims 1 to 18 in the manufacture of a medicament for treatment or prevention of a prostaglandin mediated disease.

27. A compound, salt, hydrate or ester as defined in any one of claims 1 to 18 for use in the treatment or prevention of a prostaglandin mediated disease.

28. A prostaglandin antagonist pharmaceutical composition comprising an acceptable prostaglandin antagonistic amount of a compound, salt, hydrate or ester as defined in any one of claims 1 to 18, in association with a pharmaceutically acceptable carrier.